riodic densities; and (iii) wide cleft junctions, characterized by a thick, continuous undercoating of the photoreceptor membrane and a regular (16 nm wide) cleft which usually contains periodic densities (*13*). Narrow and wide cleft junctions in goldfish are entirely different and readily distinguishable (*15, 16*).

We sectioned 17 Golgi-stained mixed bipolars (at least two of each subtype) serially through their contact with photoreceptor cells and examined them in the electron microscope. Both the type and extent of junctions are characteristic for each bipolar cell subtype, independent of photoreceptor type. Type a1 bipolars make extensive wide cleft junctions with rods (Fig. 2A) and cones. Type a2 bipolars make minimal wide cleft junctions with rods and cones. Type b1 bipolars make extensive narrow cleft junctions with both receptors and frequently ribbon contacts with rods (Fig. 2B). Type b2 bipolars make less extensive narrow cleft junctions and often terminate near the synaptic ribbon in cones as well as rods. Type b3 bipolars make minimal or no narrow cleft junctions and usually end near the ribbon in rods and cones.

These observations show that type a (hyperpolarizing, off-center) bipolars make only wide cleft junctions, unassociated with ribbon synapses, with both rods and cones, whereas type b (depolarizing, on-center) bipolars make only ribbon contacts or narrow cleft junctions (or both) with both rods and cones. It is reasonable to suppose that these specialized appositions represent the sites which mediate chemical synaptic transmission from photoreceptor to bipolar cell (*15*). Goldfish type a bipolars appear homologous to mammalian "flat" cone bipolars, and goldfish type b bipolars to mammalian "invaginating" cone bipolars (*5, 17, 18*). Our findings support the hypothesis, drawn indirectly from freeze-fracture studies of synaptic membranes in retinas and brains of different species (*18*), that the synapses upon "flat" bipolars are "excitatory" or sign-conserving whereas the synapses upon "invaginating" bipolars are "inhibitory" or sign-inverting (*13*). It remains for further studies to test the predictive value of the correlations between synaptic structure and function reported here (*19*).

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14. We have adopted cell names consistent with the nomenclature of (*6*). Types a1, a2, b1, b2, and b3 correspond, respectively, to types 5, 4, 1, 2, and 3 of (*13*), and types B1, B2, A1, A2, and A3 of (*11*).
15. A. Lasansky [*Philos. Trans. R. Soc. London Ser. B* **262**, 365 (1971)] described two forms of "basal junction" (BJ) (nonribbon contact) between cones and unidentified bipolars in turtle retina. Truly basal (superficial) BJ's in turtle appear identical to goldfish wide cleft junctions, whereas invaginated BJ's present "narrow-gap segments" which appear identical to goldfish narrow cleft junctions. The intermingling of wide and narrow features described in invaginated turtle BJ's is not observed in goldfish. We have avoided the term "basal junction," (i) because many junctions to which the term might be applied are not basal in location and (ii) because we wish to avoid any implication that wide and narrow nonribbon junctions might be identical [see also (*16*)].
16. A. R. Nagy and W. K. Stell (in preparation) have shown by freeze-fracture and replication of membrane interiors that characteristic aggregates of particles are present in goldfish bipolar cell membranes at wide cleft junctions but not at narrow cleft junctions or ribbon contacts.
17. A. Lasansky [*Invest. Ophthalmol.* **11**, 265 (1972)], observed apparently narrow-type junctions between receptors and invaginating bipolars en route to ribbon contacts in monkey retina, and Raviola and Gilula (*18*) observed no intramembrane particle aggregates in invaginating bipolars.
18. E. Raviola and N. B. Gilula, *J. Cell Biol.* **65**, 192 (1975).
19. A. Kaneko [*J. Physiol. (London)* **235**, 133 (1973)], has described "color-opponent" (R-center, R+G surround) and "noncolor-opponent" (R center, R surround) on- and off-center bipolar cells in goldfish. Assuming some of these to be mixed rod-cone bipolars, it is reasonable to suppose that type a1 and b1 cells are noncolor-opponent, since they have no apparent connection with either G cones or green-controlled horizontal cells (*7*); a2, b2, and b3 cells might then be color-opponent. Analyses of rod connectivity indicate that the absolute and relative contributions of rod activity to bipolars vary markedly with subtype [Table 1 and (*8, 12*)], as do the probable contributions of rod horizontal cells to their receptive fields (*10, 13*). Studies of the physiology and morphology of dye-injected cells, however elegant, have not yet provided sufficient data to test these hypotheses.
20. We thank E. V. Famiglietti, Jr., A. Kaneko, and M. Tachibana for sharing and discussing the results of their experiments with us, and for offering comments on this report. D. Bougn and A. Williams prepared the manuscript. Supported by grants EY 00331 and EY 01190 from National Institutes of Health.

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Body Weight: Reduction by Long-Term Glycerol Treatment

Abstract. *Elevation of body glycerol concentration by multiple daily injections of glycerol was shown to lead to hypophagia and body weight loss followed by normal food intake and normal rate of body weight increase in rats. Termination of injections was followed by hyperphagia and an accelerated rate of growth. These findings suggest that the blood glycerol concentration plays an important role in the control of body weight and may be one signal by which the central nervous system monitors body lipid content.*

It is generally believed that body weight is a regulated variable, and it has often been suggested that the regulation is achieved by the control of body lipid content (*1*). If this is the case, then the system which controls body weight must be able to sense the size of the adipose tissue stores, or some correlate of it, in order to correct deviations from "normal." There is accumulating evidence that a humoral signal might be utilized for this purpose. Studies involving the cross circulation of blood between pairs of rats, either by means of the parabiotic preparation (*2*) or by blood mixing in nonjoined animals (*3*), have shown that the blood of normal nonfasted or of obese rats contains a factor capable of suppressing food intake in a recipient animal.

The nature of a humoral signal which could be involved in the regulation of body weight through the control of food intake is unknown, but evidence exists which suggests that glycerol may be involved. A number of investigators have reported a positive relation between adipose cell size and blood glycerol concentrations (*4*). Since under some circumstances variations in body lipid content can be accounted for by variations in adipose cell size (*5*), blood glycerol concentrations in nonfasted animals should be directly related to the total lipid content of the body. If glycerol actually functions as an indicator of body lipid content, then raising the blood glycerol concentration should lead to a reduction of body weight to a new, lower settling point (*6*), at which it should be regulated. This follows from the assumption that an increase in blood glycerol would be interpreted by a control system as an increase in fat cell size and thus an increase in body weight. A body weight control system would then be expected

to temporarily activate compensatory mechanisms (for example, reduce food intake, increase energy expenditure, or decrease efficiency of nutrient utilization) to bring body weight down to within its normal range. Evidence consistent with this has been reported by Deichmann (*7*), who showed that long-term application of an aqueous solution of glycerol to the skin of rabbits prevented body weight increase during the period of application; by Lin *et al.* (*8*), who showed that oral ingestion of extremely large amounts of glycerol (43 percent of dietary energy) depressed food intake and growth rate in rats and chickens; and very recently by two studies which showed that glycerol administered either intravenously or intraperitoneally reduced food intake in rats and rabbits (*9*). Once body weight has reached a new settling point, food intake, energy expenditure, or efficiency of food utilization would be expected to return to normal and body weight should then be controlled at this new lower level. When glycerol treatment is stopped, the reverse process would be expected to occur and compensatory mechanisms should then return body weight to its previously regulated level. We report here results consistent with these predictions.

In our first experiment we examined the effect on body weight of glycerol injections and of alterations in the fat content of the maintenance diet. The subjects used throughout were male albino rats bred locally from Charles River stock. Two groups of six rats, matched for body weight, were maintained in a constant-light environment throughout the experiment. Each day at 6 a.m. and 6 p.m. the members of one group (mean body weight, 417.0 ± 7.1 g) received a glycerol (Fisher, laboratory grade) injection (40 mg/kg, 40 mg/ml) (*10*), while the members of the other group (mean body weight, 415.3 ± 8.7 g) received an approximately equicaloric (0.06 kcal) glucose injection (40 mg/kg, 40 mg/ml). All injections were given subcutaneously on the back between the scapulae. The animals were weighed daily at 3 p.m. For the first 12 days of this treatment, they were maintained on standard laboratory chow (Wayne Laboratory Diet). On day 13, this diet was replaced with a high-fat diet (two parts ground laboratory chow to one part Crisco), which they were fed for the following 14 days. The high-fat diet was used to determine whether the glycerol-treated animals would show the same accelerated rate of body weight gain typically found in rats maintained on such a diet. Positive evidence would

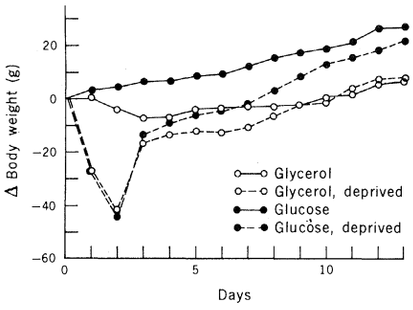

Fig. 1. Changes in body weight for the two groups of animals (glucose- or glycerol-treated) in the first two experiments described in the text.

suggest that glycerol was not making them sick; it would also suggest that the glycerol-treated animals were regulating their weight in the same way as untreated animals, but at a lower than normal level.

The results of the first part of this experiment are shown in Fig. 1. The group of animals treated with glucose showed a gradual increase in body weight at a rate of 2.6 g/day. In contrast, the animals receiving glycerol showed an initial decline in body weight followed by a period of weight gain. On the last 5 days shown in Fig. 1 the glycerol-treated animals grew at a rate of 2.2 g/day. Since the glycerol-treated rats gained weight at approximately the same rate as the glucose-treated rats once the new lower level of body weight was achieved, it appears that they were regulating their body weight but at a lower than normal level. On the day before the high-fat diet was introduced, the glycerol-treated animals had gained 5.7 ± 4.8 g while the glucose-treated animals had gained 25.8 ± 4.8 g. This difference is statistically significant ($t = 2.47$; d.f. = 10; $P < .05$).

The high-fat diet produced an immediate increase of about the same magnitude in the rate of body weight gain in both groups of animals. Regression equations fit to the rats' growth curves during the first 5 days of access to the high-fat diet showed that the glucose-treated animals gained weight at a rate of 3.9 g/day (a 67 percent increase in their rate of growth) and that the glycerol-treated animals gained weight at a rate of 3.7 g/day (a 59 percent increase in their rate of growth). At the end of this treatment, the mean increase in body weight (measured from the beginning of the experiment) of the glycerol-treated animals was 39.0 ± 10.8 g and that of the glucose-treated animals was 62.5 ± 7.0 g. Analysis of variance of the body weights of the two groups while they were ingesting the high-fat diet revealed a significant difference in body weight ($F = 7.08$; d.f. = 1,60; $P < .02$).

If elevation of glycerol concentration causes rats to regulate their body weight at a lower level, then glycerol-treated animals would be expected to defend their lowered weight against challenges. Thus if body weight is reduced by deprivation, glycerol-treated animals should return to a lower body weight level than glucose-treated animals when food is again made available. In our next study we examined this prediction. Two groups of rats closely matched in weight to the original groups were deprived of food, but not water, for 48 hours. On the day food was returned, one group received glucose injections (mean body weight before deprivation, 419.7 ± 11.7 g) and the other glycerol injections (mean body weight before deprivation, 421.3 ± 10.5 g) in the same amount and on the same schedule as in the first experiment. These injections were continued for the following 11 days and body weight was recorded daily. The results appear in Fig. 1. On the first day of recovery from deprivation, the animals in both groups recovered almost identical amounts of weight. From that point on, the growth curves of the glycerol- and glucose-treated animals separated and began to approach the curves describing the weight changes of the glycerol- and glucose-treated animals in the original experiment. Analysis of variance of the body weights for deprived and nondeprived glucose- and glycerol-treated animals on day 12 of glycerol treatment revealed a significant glycerol effect ($F = 6.88$; d.f. = 1,20; $P < .025$) but no significant difference between the previously deprived groups and nondeprived groups ($F < 1$) and no significant interaction ($F < 1$).

We next looked at the effect of glycerol treatment on food and water intake. A group of six rats (mean weight at beginning of experiment, 351 g) maintained on a 12-hour light-dark cycle was adapted for 6 days to a pelleted diet (*11*). Measurements of food and water intake and of body weight were made at approximately 4 p.m. On day 7 and for the following 5 days, they were given subcutaneous injections of glucose (40 mg/kg, 40 mg/ml) at 6 p.m., midnight, 6 a.m., and noon. On day 12, the animals were injected with glycerol (40 mg/kg, 40 mg/ml) rather than glucose at the same times that glucose had been administered previously. Glycerol injections were continued four times a day for 9 days, after which all injections were discontinued, but body weight and food and water intake were measured for the following 9 days.

The results of this experiment are shown in Fig. 2, which summarizes the

change in body weight, and the daily food and water intake of the animals in this experiment. As in the other experiments reported here, glycerol, but not glucose, injections produced a significant (t = 2.83; d.f. = 5; $P < .05$) reduction in body weight from 385.2 ± 13.6 to 378.6 ± 13 g followed by a period of normal weight gain. Food intake following the initiation of glycerol treatment showed a significant decrease from 98.6 ± 7.2 to 79.1 ± 7.1 kcal in response to glycerol treatment ($t = -3.56$; d.f. = 5; $P < .05$), as did water intake ($t = -2.55$; d.f. = 5; $P < .05$) from 35.5 ± 2.7 to 28.8 ± 1.7 ml. Thereafter, food and water intake gradually increased until they were within the normal range. When glycerol injections were terminated, food and water intake increased and rate of growth increased significantly from 2.5 to 3.8 g/day (t = 2.36; d.f. = 5; $P < .05$).

The results of this experiment indicate that one contributing factor to the reduction in body weight produced by glycerol was a hypophagia which lasted until a new lower body weight was reached. Since food intake returned to normal during glycerol treatment, the hypophagia does not appear to have been illness-induced. The hyperphagia which occurred when glycerol treatment was terminated resulted in an increased rate of body weight gain, suggesting the activation of a mechanism whose effect was to bring weight back to within its normal range. Since both food and water intake were reduced significantly, and since changes in food and water intakes are normally closely related, it is possible that the hypophagia was secondary to hypodipsia. Our data provide no way of determining which is the primary effect, but the relatively larger effect on food intake in comparison with that on water intake suggests to us that the hypodipsia may have been secondary to the hypophagia.

All of these results are consistent with the hypothesis that glycerol plays an important role in the control of body weight. The fact that glycerol, but not equicaloric glucose, reduced body weight seems to rule out the possibility suggested by Bray and Campfield (*12*) that glycerol participates in the control of body weight after its conversion to glucose. Since preliminary results from our laboratory show that continuous perfusion of cerebral spinal fluid with microgram quantities of glycerol in freely feeding rats produce results very similar to those reported here, we believe that glycerol may act centrally by providing a central nervous system (CNS) weight control mechanism with a feedback signal proportional to fat cell size and thus to body weight.

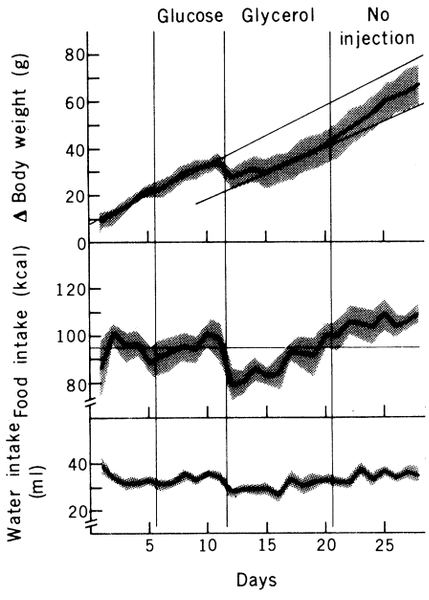

Fig. 2. Mean daily change in body weight and mean food and water intake for animals injected with glucose and then glycerol. The shaded regions cover ± 1 standard error. The two parallel solid lines drawn through the means of the changes in body weight are the regression lines for the change in body weight during the first 11 days of the experiment and during the last 5 days of glycerol treatment, respectively. The equations are $y = 2.5x + 8.2$ and $y = 2.5x - 8.0$, respectively, indicating equal rates of growth during these periods. The horizontal line in the food intake graph describes the mean food intake during the time preceding glycerol treatment.

The results also raise the possibility that the stimulation or inhibition of food intake and body weight by a number of compounds may be mediated through their action on blood glycerol levels. For example, noradrenaline, glucagon, and theophylline, which have been shown to suppress food intake (*13*), also increase glycerol output (*14*). On the other hand, insulin, which stimulates food intake (*15*), inhibits lipolysis causing a reduction in blood glycerol levels (*16*). The possibility that insulin increases food intake through reduced glycerol levels is also supported by the finding that glycerol is more effective than glucose in blocking insulin-induced feeding (*16*).

Finally, while suggesting a role for glycerol in the control of body weight, our results raise some problems. In the second experiment reported here, food-deprived rats given glycerol gained as much weight on the first day of recovery from deprivation as did rats given glucose. It is well known that 48 hours of food deprivation significantly elevates blood glycerol in rats. Why then does this high level of glycerol not inhibit food intake in deprived rats given access to food? One possible explanation is that the CNS responds to a pattern of humoral signals rather than a single one alone and does not inhibit food intake in the presence of elevated blood glycerol levels when, for example, blood glucose and insulin levels are low and ketone body and fat-mobilizing substance (*17*) levels are high, indicating a state of deprivation. Another question posed by these results is why obese patients who have high blood glycerol levels maintain their elevated body weight. A possibility is that the CNS mechanisms responsible for detecting glycerol may be abnormally insensitive to glycerol or do not read the signal correctly in such individuals.

Although we can only speculate at this time about how a weight control system operates during starvation and in abnormal states such as obesity, our results suggest that in the normal nonstarved rat blood glycerol levels may play a much more important role in the control of body weight and food intake than has been demonstrated in the past.

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Methylphenidate in Hyperkinetic Children: Differences in Dose Effects on Learning and Social Behavior

Abstract. *Methylphenidate (Ritalin) is widely prescribed for hyperkinetic children. This study showed a peak enhancement of learning in children after being given a dose of 0.3 milligram per kilogram of body weight, and a decrement in learning in those given larger doses; social behavior showed the most improvement in children given 1.0 milligram per kilogram. These results had been hypothesized from theoretical dose-response curves which indicate different target behaviors would improve at different doses.*

Methylphenidate (Ritalin) is a stimulant drug prescribed extensively to alter the behavior of schoolchildren. There is general agreement that it improves attentional behavior and decreases impulsivity in hyperkinetic children (*1*). Although dose-response curves are usually obtained in animal psychopharmacological research (*2*), there has been little systematic study of dose-response effects of psychoactive drugs on different target behaviors in children (*3*). There have been few attempts to determine whether the optimum dose of methylphenidate for improvement in attention which results in better learning varies from that considered optimum for improvement in social behavior in the classroom. We have postulated theoretical dose-response curves on a milligram per kilogram basis for different target behaviors (*4*), and have theorized from data accumulated from experiments with a more restricted dosage range that low doses of methylphenidate lead to the maximum enhancement of learning performance, whereas much larger doses are required to maximize improvement in social behaviors. The study described herein provided an empirical test of the theorized dose-response curves as measured by target behaviors of learning performance, social behavior, and cardiovascular side effects (*5*).

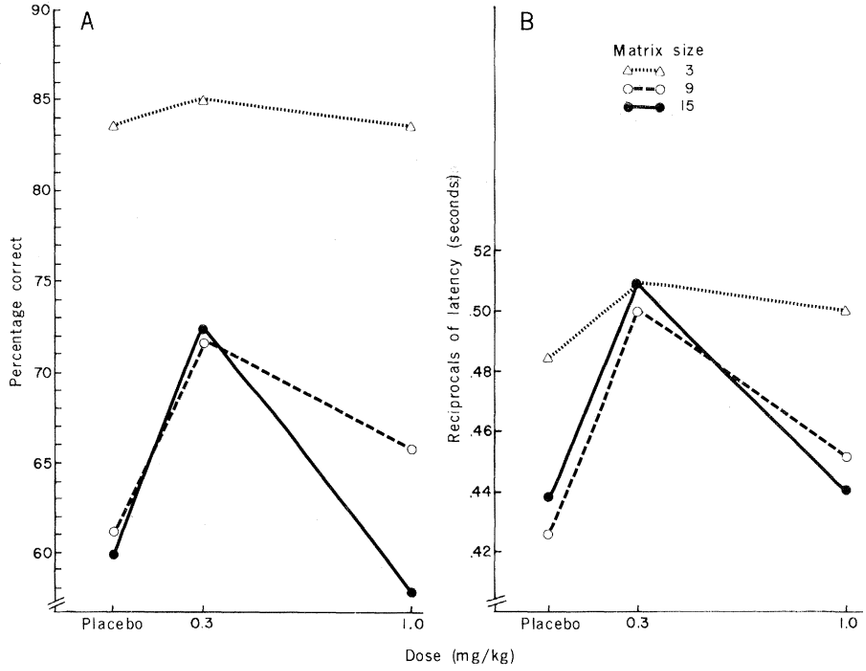

Fig. 1. Dose-response curves for (A) accuracy and (B) latency obtained at differing levels of information load (matrix size) for hyperactive children taking methylphenidate.

All children accepted for our pediatric psychopharmacology project are thoroughly screened. The score they obtain on the Conners' Teacher Rating Scale (*6*) must be 2 standard deviations above the normal mean (*7*, *8*), the pediatric examination must be negative for other major diseases, there must be no indications of serious family pathology on the basis of their social history, and the parents must give their written informed consent. These studies always involve a crossover design with placebo control, strict double-blind conditions, and measures from several behavioral and physiological domains. The capsules (which conceal the contents) containing the methylphenidate tablets are packaged by the pharmacist and then placed in dated envelopes to ensure that the parent actually administers the assigned dosage at the proper time. Additional experimental procedures are described elsewhere (*3*, *9*).

Numerous measures of learning, social behavior, cardiovascular functioning, and psychophysiological function are taken during an intensive 9-week study period. Only the learning, social behavior, and heart rate measures will be described here. The test of short-term memory requires the child to look briefly at a matrix of children's pictures, then respond a few seconds later to a test picture, and indicate whether the test picture was presented previously or not (*3*, *4*). Different numbers of pictures (3, 9, and 15) were included in the presentation matrix; the larger number of pictures increases the information load. Accuracy of recognition, latency of responding to the test pictures, and amount of wiggling on a stabilimetric cushion (*10*) were automatically recorded. The learning performance task was given at the end of each 3-week dosage period 1.5 hours after oral administration of the dose the child had been taking for that period. At the end of each school week the child's classroom teacher completed an Abbreviated Conners' Rating Scale (*11*). We consider this scale to be a measure of the problematical social behavior of the child in the classroom. When the child came to the laboratory for the learning task, the research pediatrician (E.K.S.), about 1.5 hours after the child ingested the capsule, recorded the heart rate after the child had rested for 5 minutes (*5*). Heart rate was obtained with a stethoscope placed over the precordium and was measured for 1 minute with the child seated. Three dosages of methyl-